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EFFECT OF SUSPENDING AGENTS ON THE BIOAVAILABILITY OF ERYHTROMYCIN ETHYLSUCCINATE MIXTURES

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ABSTRACT

The effect of the suspending agents sodium carboxymethylcellulose, bentonite and agar on the bioavailability of erythromycin ethylsuccinate mixtures has been studied in twelve healthy volunteers. Bentonite and agar reduced the absorption whereas sodium carboxymethylcellulose seemed to improve it. Drug-additive interaction could account for the observations and possible mechanisms are discussed.

INTRODUCTION

Oral aqueous suspensions (mixtures) form an important class of pharmaceutical dosage forms especially in

pediatrics. Because all such systems separate on standing the mixture must be easily resuspendable and remain sufficiently homogenous for at least the period of time necessary to remove and administer the required dose.

The consistency of suspensions is usually accomplished by incorporation of suspending agents, e.g., hydrophilic polymers such as sodium carboxymethylcellulose or certain water-insoluble hydrophilic materials such as bentonite or colloidal silica. In many cases the adjuvants are compatible with the active ingredient but one must always be on guard against possible drug-additive interaction which may, among other undesirable consequences, lead to poor bioavailability of the product.

When formulating antibiotic-containig suspensions for pediatric use this aspect is naturally very important, e.g., rifampicin activity is reduced by bentonite (1) and neomycin is adsorbed by this and other clays (2,3).

The objective of the present studies was to evaluate the influence of certain suspending agents: sodium carboxymethylcellulose (CMC), bentonite and agar on the relative bioavailability of erythromycin ethylsuccinate mixtures. The question arose as a consequence of observations during the product development.

EXPERIMENTAL

Materials

Erythromycin ethylsuccinate (Lot E-ES/095, Archifar, Trento, Italy), the suspending agents - CMC (7MF, Hercules N.V., Wilmington, Delaware, USA), bentonite (Veegum, pharm., R.T. Vanderbilt Co, New York, NY, USA) and agar (Ph. Nord. quality, Knut Henberg, Helsinki, Finland), and sorbitol (B.P. quality, Suomen Sokeri, Kotka, Finland) were all commercial products. Water was double distilled and sterilized. Other chemicals were of analytical grade (E. Merck, Darmstadt, BDR).

Sample preparation

All preparations contained 4.91 w/v% of erythromycin ethylsuccinate (corresponding to 4.0 w/v% of erythromycin), 45 w/v% of sorbitol and 2 w/v% of sodium citrate. The pH of the mixtures was about 8.3. The concentrations of the suspending agents varied as follows: CMC 1.0 w/v%, bentonite 1.0 w/v% and agar 0.35 w/v%. The rheological behaviour of different mixtures was very similar when determined by a rotating viscometer (Rotovisko RU 3, Gebrüder Haake, Karlsruhe und Berlin, BDR) and thus the possible influence of different viscosities could be avoided.

Bentonite and CMC mixtures were prepared by slurrying the additives with solution containing sorbitol and sodium

citrate and allowing the mixtures to stand for 24 hours. Thereafter erythromycin ethylsuccinate was dispersed into the mixture. Finally, the formulation was shaken for 4 hours (type VT, Erweka GmbH, Frankfurt am Main, BDR). Agar was dissolved in the before mentioned solution by warming until it was clear. After 24 hours standing the suspension was prepared similarly to the others.

The control mixture, called aqueous suspension, was made without any suspending agent.

Trial conditions

Twelve normal, healthy subjects, eleven females and one male ages 18 to 43 years and weighing from 53 to 90 kg participated in the study. They had taken no medication in, at least, the previous 7 days.

The formulations were administered with about 100 ml of tap water after an overnight fast. No food or liquids were taken during the first two hours following administration.

The dose corresponded to 400 mg of erythromycin. Blood samples were withdrawn into sterilized tubes before drug administration and at 0.5, 1, 2 and 4 hours after the dose. The samples were centrifuged, the plasma separated, stored at $+4^{0}$C and analyzed for erythromycin concentrations on the same day.

Measurement of erythromycin

Erythromycin concentrations in serum were determined microbiologically by an agar-diffusion using medium 1 (4). Sarcina lutea AT CC9341 was the test organism. Erythromycin base USP standard (5) was prepared in identical fashion to the test specimens.

Calculations

The area-under-the-curve (AUC_{0-4h}) was calculated by the trapezoidal rule. For statistical analysis paired t-test was employed.

RESULTS

From the mean serum concentrations shown in Fig. 1 it seems that erythromycin ethylsuccinate is rapidly absorbed from gastrointestinal tract. Maximum serum levels are achieved in 1 to 2 hours. Elimination is also rapid, after 4 hours no trace of erythromycin was detected in serum.

The various formulations show very varying concentration-time curves. At 1/2 and 1 hours the erythromycin concentrations obtained with CMC suspension are significantly higher than those of bentonite or agar suspensions ($p < 0.01$ and $p < 0.001$, respectively). The differences become smaller with time but are significant ($p < 0.01$) between agar and CMC suspensions also at 2 and 4 hours.

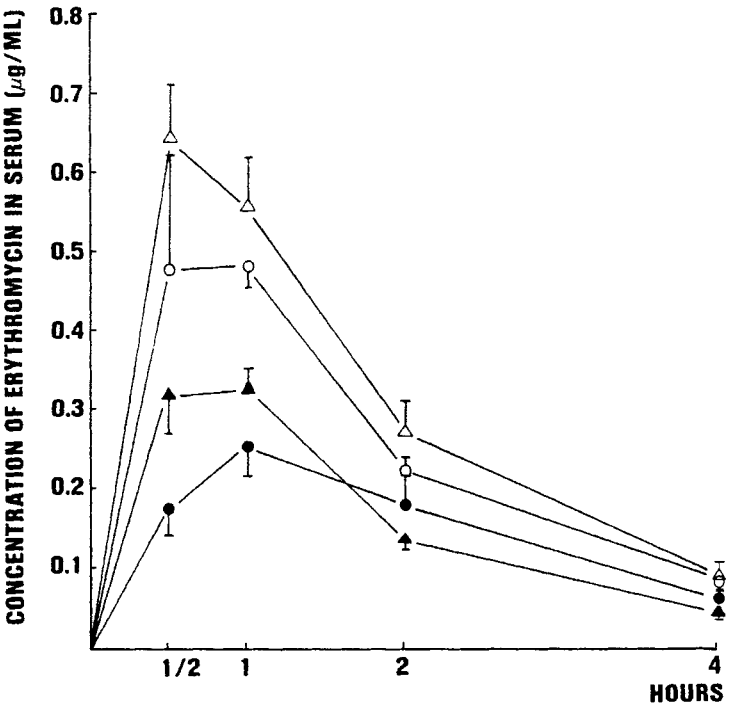

FIGURE 1.

SERUM CONCENTRATIONS OF ERYTHROMYCIN (μg/ML±SE) AFTER ORAL ADMINISTRATION OF VARIOUS FORMULATIONS.

○-○ AQUEOUS SUSPENSION △—△ CMC SUSPENSION

●—● BENTONITE SUSPENSION ▲—▲ AGAR SUSPENSION

CMC suspension seems to be superior to aqueous suspension although the differences between the serum concentrations are not statistically significant at any point of determination.

A comparison of bentonite and agar suspensions shows that they behave quite similarly. Only after half an hour there is a slight significant difference ($p < 0.01$) in erythromycin concentrations in serum. The AUC values (Table 1) confirm that the bioavailability of the formulations varies considerably as the CMC suspension is very significantly superior to agar and bentonite suspensions ($p < 0.01$). Other comparisons result in only slight difference ($p < 0.05$) between bentonite and aqueous suspensions.

DISCUSSION

From the results it seems that CMC is the most suitable of the suspending agents studied. It seems to even enhance the absorption of erythromycin ethylsuccinate. The other excipients, agar and bentonite have a detrimental influence on the bioavailability of the antibiotic.

Since the rheological behaviour of the suspensions studied was quite similar, the possible influence of different viscosities on the bioavailability can be excluded. Thus, drug-additive interaction may explain the results obtained.

Recently, interactions between CMC and drugs have been the subject of rather intensive research work.

TABLE 1.

$AUC_{(0-4h)}$ Values for Different Formulations

Subject	$AUC_{(0-4h)}$ $mg \cdot h \cdot l^{-1}$			
	Aq. susp.	Bentonite	Agar	CMC
LK	-	0.548	0.618	1.100
MJ	-	0.735	0.533	1.484
RS	-	0.514	0.983	2.029
KU	1.228	0.580	0.349	0.887
ML	-	1.460	0.646	0.754
TS	-	0.858	1.088	1.380
PR	0.970	0.700	0.611	1.462
MA	-	0.172	0.825	0.682
MK	-	0.577	0.625	1.572
LS	-	0.433	0.492	1.162
PL	0.827	0.180	0.428	0.499
AV	0.746	0.410	0.787	2.045
Mean	0.943	0.597	0.665	1.255
± SD	0.212	0.340	0.220	0.500
± SE	0.106	0.098	0.063	0.144

According to the results of these studies the complexing ability of this polyelectrolyte is due to ionic binding and hydrophobic interaction (6-9). This, however, does not explain why CMC in our study seems to be superior to aqueous suspensions because retardation of drug absorption is a normal consequence if a drug complexes with macromolecules.

Higuchi et al. have demonstrated that CMC enhances the absorption of drugs such as sodium salicylate and potassium benzylpenicillin (10). Thus, the absorption of anionic drugs may be increased by anionic polyelectrolytes.

At present, we do not have a definite idea how erythromycin ethylsuccinate (Fig. 2) behaves in the above system. It is known that the amino group of this antibiotic may be protonated and complexed with the anion of CMC but this should retard drug absortion. On the other hand, erythromycin ethylsuccinate might, owing to its hydroxyl groups, behave like an anion which could explain the enhanced transfer through gastrointestinal membranes.

Another explanation is that the wettability of erythromycin ethylsuccinate is enhanced due to the interaction. When the antibiotic particles are covered by CMC, orientating the hydrophilic moieties towards the solution,

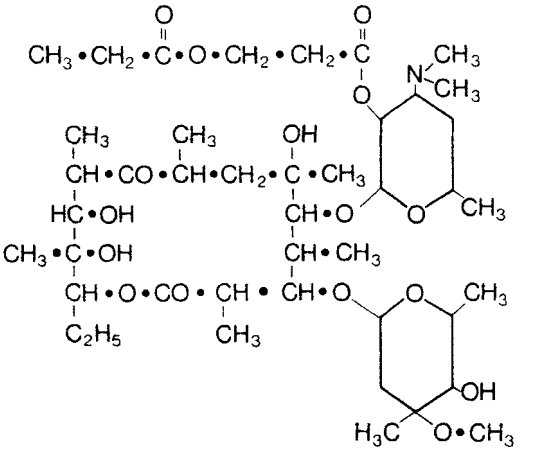

FIGURE 2.

THE STRUCTURE OF ERYTHROMYCIN ETHYLSUCCINATE.

the contact with water becomes enhanced and the dissolution rate increases.

Practically no information is available in the literature on the interaction between drugs and agar. This macromolecule is composed of two polysaccharides and has an ionic character due to free acidic groups in the molecule. The reduced bioavailability of agar suspensions might arise from the interaction between the protonated amino group of erythromycin ethylsuccinate and the sulphuric acid groups of the polyelectrolyte. Also, hydrophobic interaction could have some influence.

In contrast to agar the literature gives quite a good insight into the drug-bentonite interaction. The

main component of this mineral is montmorillonite, a complex colloidal magnesium aluminium silicate which is able to ion exchange and has adsoptive properties. It is also capable of entrapping organic molecules mechanically between the silica layers (11-15). In most cases the interaction must be considered as undesirable but sometimes it could be employed to prolong the action of cationic drugs (16).

UV and IR techniques were used by Berkheimer and Alrich to study the adsorption of a herbicide, 3-amino-2,5-dichlorbenzoic acid, to bentonite (14). They concluded that the protonation of the amino group and the hydrogen bond formation between the carboxyl group and the hydration water layer of the interlayer cation of bentonite are the interaction mechanisms. Accordingly, the amino group of erythromycin ethyl-succinate may be protonated and hydrogen bonded through its hydroxyl groups at the montmorillonite surface.

An interesting way to explain the reduced bio-availability of bentonite mixture may be based on the proposal by Rupprecht (15), that codeine, in aqueous milieu, is antrapped mechanically by bentonite. There is also van der Waals' interaction between the pro-tonated amino group and the negatively charged centers of the silica layer, hydrogen bonds through the hydr-oxyl and amino groups to the oxygen atoms and, finally,

the methoxy group of codeine is suitably large in size to fit into the cavities of the silica layers. These cavities are a result of the structure of the $(SiAl)O_4$ tetrahedrons. Because erythromycin ethylsuccinate molecule has exactly the same groupings - amino, hydroxyl and methoxy groups (Fig. 2) - it is tempting to explain the observed interaction similarly.

Unfortunately, we have, at the moment, no results of *in vitro* experiments to evaluate the binding mechanisms and capacities of the excipients but such experiments are in progress.

Whatever the mechanisms of interaction, the present investigation demonstrates the undesirable effects of bentonite and agar on the bioavailability of erythromycin ethylsuccinate mixtures and, on the other hand, that this property of oral suspensions might be improved by proper choice of suspending agents.

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